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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,981	03/22/2001	Gary DeJong	24601-416B	7622

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/16/2002

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/815,981	DEJONG ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This is a First Office Action on the Merits of the application filed March 22, 2001. This Office Action is a response to the "Election and Preliminary Amendment" filed October 17, 2002 (Paper No. 18). Claims 17-29, 31 and 32 were canceled in Paper No. 18. Claims 1-16 and 30 are pending and under consideration in the application.

Election/Restrictions

In response to the Restriction Requirement mailed September 19, 2002 (Paper No. 17) Applicant has amended claim 9 such that claims 9 and 10 are now properly directed to the Invention of Group I as set forth in Paper No. 17 and has canceled all claims directed to the Invention of Group II. Although not explicitly stated in Paper No. 18, this response will be treated as an election without traverse of the Invention of Group I.

Claim Objections

Claims 1, 3 and 30 objected to because of the following informalities: claim 1 is missing an article in line 2, there is no period at the end of claim 3 and claim 30 recites the plural "cells" in line 3 where the singular would be more appropriate. Appropriate correction is required.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-8, 11-16 and 30 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-8, 11-16 and 30 of copending Application No. 10/086,745. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The cited claims in application 10/086,745 are identical in scope to the claims of the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior

art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention: The claims of the instant invention are directed to a method for detecting or determining the delivery and expression of a nucleic acid introduced into a cell comprising introducing a labeled nucleic acid molecule encoding a reporter gene into a cell and measuring the product of the reporter gene.

State and level of predictability in the art: Teachings in the prior art published as recently as late 1999 indicate that obtaining expression from a labeled nucleic acid molecule is highly unpredictable. Felgner *et al.* (1999) WO 99/13719 teaches that standard methods of labeling DNA using fluorescently tagged nucleotides do not allow detection of structurally and functionally intact plasmid in a real-time fashion in viable cells (paragraph bridging pages 1 and 2) and that "all of the technologies...for chemically modifying plasmid DNA result in DNA damage and interfere with its transcriptional activity" (sentence bridging pages 1 and 2). Neves *et al.* (2000; published online December 15, 1999) *Bioconjugate Chem.* 11:51-55 demonstrated that reporter gene expression was greatly reduced by labeling DNA with *p*-azido-tertrafluorbenzylamido-lissamine and abolished by labeling DNA with rhodamine labeled nucleotides (see especially the fourth full paragraph on page 53, and Figure 2 and the caption thereto). Neves *et al.* suggests that the poor expression obtained with labeled vectors might result from interference with the transcription apparatus (see especially the fourth paragraph in the second column on page 54) or sequestration or degradation of the labeled molecules (see

especially the first paragraph on page 55). Zelpahti *et al.* (1999) *Hum. Gene Therap.* 10:15-24 teaches that, "the methods that have been employed to directly modify DNA either reduce or destroy its ability to be transcribed. In addition, the available approaches to chemically modify plasmid, which utilize photolysis, nick translation, or the use of chemically active nucleotide analogs, attack the DNA randomly so that the final product is chemically heterogeneous and poorly defined" (paragraph bridging pages 15 and 16).

These teachings from the relevant art demonstrate that obtaining expression of a gene from a nucleic acid molecule that has been chemically modified to incorporate a label was highly unpredictable at the time the instant application was filed.

Amount of direction provided by the inventor and existence of working examples: In statements that can be found throughout the instant disclosure (see especially the first and second full paragraphs on page 33), Applicant teaches that nucleic acid molecules can be labeled by incorporation of nucleic acid analogs. Applicant then states that studies performed with ACes comprising a GFP reporter gene and labeled with IdU "have revealed that incorporation of the analog label does not affect GFP protein expression" (first full paragraph on page 35). However, no data is provided to support this assertion, which is at odds with the teachings of the prior art, therefore it is unclear whether this is a statement of fact or a prophetic statement.

In Example 7, Applicant teaches a method of labeling ACes carrying a beta-galactosidase reporter gene with IdU or BrdU and transfection of cells by the labeled ACes. Applicant then states that colonies were assayed for reporter gene expression (final sentence on page 54) but provides no evidence to indicate that expression was detected. Given the strong teachings from the prior art indicating that incorporation of labeled nucleotide analogues adversely affects

expression from the labeled DNA, and the absence of evidence to the contrary, the skilled artisan would not predict that expression was detected in these assays.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is very high, teachings in the relevant art indicate that obtaining expression from a nucleic acid labeled according to the teachings of the specification is highly unpredictable. The disclosure fails to provide any evidence that the methods described therein are any more effective than the methods already available in the prior art. Therefore, in order to practice the claimed invention, the skilled artisan would have to resort to trial and error experimentation to develop techniques that would enable reporter gene expression from labeled nucleic acids produced according to the teachings of the specification. Given the art-recognized unpredictability in obtaining expression from labeled nucleic acids, the degree of experimentation required would certainly be undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is indefinite in its reference to "step (a)" in line 1, there is no antecedent basis for step (a) in claims 1 or 6, from which claim 9 depends.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 6-10, 12, 14-16 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Felgner *et al.* (*supra*).

Claims 1, and 2, 4, 6-10, 12, 14-16 and 30, as they depend from claim 1, are directed to a method for detecting or determining delivery and expression of a nucleic acid introduced into a cell comprising: introducing labeled nucleic acid molecules that encode a reporter gene into cells; detecting labeled cells as an indication of delivery of the nucleic acid onto a cell; and measuring the product of the reporter gene.

Felgner *et al.* teaches a method for detecting or determining delivery and expression of a nucleic acid introduced into a cell comprising: introducing labeled nucleic acid molecules that encode a reporter gene into cells; detecting labeled cells as an indication of delivery of the nucleic acid onto a cell; and measuring the product of the reporter gene (see especially the second full paragraph on pages 2 and 3).

Claim 2 limits the method of detection of labeled cells to cell imaging or flow cytometry; claim 4 limits the nucleic acid molecule to DNA; claim 6 limits the reporter gene to a gene encoding a fluorescent protein, enzyme or antibody; claim 7 limits the enzyme of claim 6 to a luciferase, a β-galactosidase or an alkaline phosphatase; and claim 8 limits the fluorescent protein of claim 6 to a red, green or blue fluorescent protein.

Felgner *et al.* teaches the method wherein detection of labeled cells by fluorescence microscopy (see especially the third full paragraph on page 7), the labeled nucleic acid is DNA, the reporter gene is a fluorescent protein or enzyme selected from green fluorescent protein,

luciferase, β-galactosidase or alkaline phosphatase (see especially the first full paragraph on page 3).

Claim 9 limits the introducing step of claim 1 to comprising contacting the nucleic acid molecule with a delivery agent that comprises a cationic compound; claim 10 limits the cationic compound of claim 9 to one of various compounds.

Felgner *et al.* teaches the method wherein the molecule is contacted with a delivery agent that comprises a cationic compound selected from the list of compounds set forth in claim 10 (see especially the second paragraph on page 10 and U.S. Patent Nos 4,897,355 and 5,459,127 incorporated by reference therein).

Claim 12 limits the nucleic acid molecules of claim 1 to plasmids; claim 14 limits the cells of claim 1 to eukaryotic cells; claim 15 limits the cells of claim 14 to cell lines or animal cells; claim 16 limits the cells of claim 14 to tumor cells or transformed cells; and claim 30 limits the cells of claim 1 to an immortalized cell or a tumor cell.

Felgner *et al.* teaches the method wherein the nucleic acid molecule is a plasmid (see especially the second full paragraph on page 3), the cells are eukaryotic cells which are transformed, immortalized tumor cells (see the cells used in Example 6, especially the sixth paragraph on page 16).

The method, nucleic acid, reporter gene, delivery agent, plasmid and cells taught by Felgner *et al.* are the same as those taught in the instant application; therefore the limitations of the claims are met by Felgner *et al.*

Claims 1, 2, 4, 6, 7, 9, 10, 12 14-16 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Neves *et al.* (*Supra*).

The limitations of the claims are set forth herein above. Neves *et al.* teaches a method for detecting or determining delivery and expression of a nucleic acid introduced into a cell comprising: introducing labeled nucleic acid molecules that encode a reporter gene into cells; detecting labeled cells as an indication of delivery of the nucleic acid onto a cell; and measuring the product of the reporter gene (see especially the paragraph bridging columns 1 and 2 on page 52, the first full paragraph in the second column on page 52, and Figures 2 and 3 and the captions thereto).

Neves *et al.* further teaches the method wherein detection of labeled cells by fluorescence microscopy according to claim 2 (see especially Figure 3 and the caption thereto), the labeled nucleic acid is a plasmid DNA according to claim 4, and the reporter gene is β-galactosidase according to claims 6 and 7 (see especially the paragraph bridging columns 1 and 2 on page 52).

Neves *et al.* teaches the method wherein the molecule is contacted with a delivery agent that comprises the cationic compound RPR 120535 according to claims 9 and 10 (see especially the paragraph bridging columns 1 and 2 on page 52).

Neves *et al.* teaches the method wherein the nucleic acid molecule is a plasmid according to claim 12 (*Id*) and the cells are eukaryotic cells which are transformed, immortalized tumor cells (i.e. 3T3 cells) according to claims 14-16 and 30 (see especially the paragraph bridging columns 1 and 2 on page 52).

The method, nucleic acid, reporter gene, delivery agent, plasmid and cells taught by Neves *et al.* are the same as those taught in the instant application; therefore the limitations of the claims are met by Neves *et al.*

Claims 1, 2, 4, 6, 8-10, 12 14-16 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Zelphati *et al.* (*Supra*).

The limitations of the claims are set forth herein above. Zelphati *et al.* teaches a method for detecting or determining delivery and expression of a nucleic acid introduced into a cell comprising: introducing labeled nucleic acid molecules that encode a reporter gene into cells; detecting labeled cells as an indication of delivery of the nucleic acid onto a cell; and measuring the product of the reporter gene (see especially the section entitled "*Simultaneous detection of plasmid DNA ant its encoded protein*" beginning the first column on page 20, and figures 4 and 6 and the captions thereto).

Zelphati *et al.* further teaches the method wherein detection of labeled cells by fluorescence microscopy according to claim 2 (see especially Figure 4 and the caption thereto), the labeled nucleic acid is a plasmid DNA according to claim 4, and the reporter gene is GFP according to claims 6 and 8 (see especially the sections cited in the preceding paragraph).

Zelphati *et al.* teaches the method wherein the DNA molecule is contacted with a delivery agent that comprises the cationic compound DMRIE/DOPE according to claims 9 and 10 (see especially the caption to figure 4).

Zelphati *et al.* teaches the method wherein the nucleic acid molecule is a plasmid according to claim 12 (*Id*) and the cells are eukaryotic cells which are transformed, immortalized

tumor cells (i.e. CV-1 cells) according to claims 14-16 and 30 (see especially the paragraph bridging columns 1 and 2 on page 52).

The method, nucleic acid, reporter gene, delivery agent, plasmid and cells taught by Zelphati *et al.* are the same as those taught in the instant application; therefore the limitations of the claims are met by Zelphati *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Felgner *et al.* (*supra*) or Zelphati *et al.* (*Supra*) in view of Nolan *et al.* (2000) WO 00/34436.

The limitations of claims 1 and 2 are set forth herein above as are the teachings of Felgner *et al.* and Zelphati *et al.* Claim 3 is directed to the method of claim 1 wherein the labeled cells are detected by flow cytometry.

To summarize the teachings of Felgner *et al.* and Zelphati *et al*, each of the cited references teaches a method for detecting or determining delivery and expression of a nucleic acid introduced into a cell comprising: introducing labeled nucleic acid molecules that encode a reporter gene into cells; detecting labeled cells as an indication of delivery of the nucleic acid onto a cell; and measuring the product of the reporter gene.

The cited references teach all of the limitations of claims 1-3 except the detection of labeled cells by flow cytometry.

Nolan *et al.* teaches a method of delivering DNA into cells wherein cells that have taken up DNA are identified by flow cytometry (see especially the "Summary of the Invention" bridging pages 5 and 6). Nolan *et al.* explicitly teaches that it is preferred that the transferred DNA be fluorescently labeled (see especially the final paragraph on page 9).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Felgner *et al.* or Zelphati *et al.* to include the separation of labeled cells by flow cytometry according to the limitations of claims 2 and 3.

Motivation to combine these teachings comes from Nolan *et al.* who teaches that "[f]low cytometry methods such as fluorescence-activated cell sorting (FACS) are ideal tools to employ in chromosome insertion methods due to their ability to rapidly process and analyze large numbers of individual cells" (final paragraph on page 1).

Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings, as the flow cytometric method of Nolan *et al.* would work with any fluorescently labeled DNA.

Claims 11-13 are directed to the method of claim 1 wherein the nucleic acid molecules transferred are large DNAs including natural chromosomes and artificial chromosomes.

As set forth herein above, Felgner *et al.* and Zelphati *et al.* teach all of the limitations of the method according to claim 1. Felgner *et al.* and Zelphati *et al.* do not, however, teach the method wherein the transferred DNA is a large DNA or chromosome.

Nolan *et al.* teaches a method of delivering fluorescently labeled large DNAs into cells wherein the DNAs transferred include natural chromosome and artificial chromosomes (see especially the third full paragraph on page 8).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Felgner *et al.* or Zelphati *et al.* according to the teachings of Nolan *et al.* to deliver fluorescently labeled transcriptionally active chromosomes into cells.

Motivation to combine these teachings comes from Nolan *et al.*, who teaches "[t]he introduction of intact single chromosomes (i.e. large protein/DNA complexes) into cells offers unprecedented usefulness as a...method for generating transgenic animals. Advantages of artificial chromosomes include (1) the introduced chromosome is biologically stable in the cell...(2) chromosomes will be inherited by daughter cells following cell division; (3) integration of the introduced chromosome into pre-existing chromosomes is not likely and not necessary for stable expression of the delivered gene(s)" (second paragraph on page 1). Motivation also comes from Zelphati *et al.* who teaches that their methodology provides a means to tag DNA without disrupting the structural or functional integrity of the DNA (see especially the first full paragraph on page 16).

In the absence of evidence to the contrary, one would have a reasonable expectation of success in combining these teachings, as the methods of labeling taught by Felgner *et al.* and Zelphati *et al.* are readily applicable to any nucleic acid molecule.

Conclusion

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
December 5, 2002

JAMES KETTER
PRIMARY EXAMINER